REMARKS

Claims 1-39 and 53-62 are pending in the application. Claims 1 and 58 have been amended, and claims 54-56, 59, and 61-62 have been cancelled without prejudice. Claims 14, and 18-39 are withdrawn subject to a restriction requirement. Therefore, upon entry of the instant amendment, Claims 1-13, 15-17, 53, 57-58, and 60 will be before the Examiner.

Support for the amendments can be found in the specification and claims as originally filed. Claim 1 has been amended to recite the language of this claim essentially as originally filed. Support for the amendment of Claim 1 can be found, for example, in the specification on page 31, lines 2-3. Support for the amendment of Claim 58 can be found, for example, in the specification on page 69, lines 3-4. No new matter has been added.

In response to the request (Office Action, page 3, item 3) regarding Reference S in the Information Disclosure Statement (IDS), Applicants herein respectfully supplement the citation for the reference as follows, to provide information which was inadvertently omitted from the Form PTO/08/SB: *Invest. Ophthalmol. Vis Sci.* 33(4):Suppl., p. 866, 1993.

Rejections Under 35 USC § 112:

Claims 1-12 and 53-62 were rejected under 35 USC § 112, second paragraph,as allegedly being indefinite for use of the term "modulates" in claim 1, because according to the Office Action, it is not clear what direction of modulation (up or down) is required. Claim 1 has been amended to recite "decreases." Applicants respectfully submit that the claim as amended is not indefinite, and according request reconsideration and withdrawal of this rejection.

Claims 1-13, 15-17, and 53-62 were rejected under 35 USC § 112, first paragraph, for failure to satisfy the written description requirement. According to the Office Action, the specification and claims as originally filed do not provide support for

the invention as now claimed (new matter rejection). The Office Action (p. 4) recites four examples (A-D) of alleged new matter.

In regard to A), Claim 1 has been amended to delete the phrase "or extracellular matrix of a retina or choroid."

In regard to B), Claim 1 has been amended to recite the phrase "or protein." As discussed in the Office Action, the specification at page 31, lines 2-3, for example, provides support for the amendment, disclosing "preferred genes/proteins to be targeted." Applicants do not necessarily agree or acquiesce with the rejection, particularly because the title of the subject section on page 31 is "Agents that Modulate Expression or Activity of Phagocytosis-Related and AMDP-Related Gene Products." The term "gene product" is commonly understood by those of skill in the art of molecular biology to refer to either a nucleic acid or amino acid product encoded by a gene. Nevertheless to expedite prosecution, Applicants have amended the claim to recite the term "or protein" as disclosed in this context on page 31 of the specification.

In regard to C), claims 54-56 having been cancelled, these rejections are now moot.

In regard to D), the rejection is moot with respect to Claims 59, and 61-62, which have been cancelled. Claim 58 has been amended to recite "by injection to the eye." Specific support for the amendment can be found in the specification, for example, at page 69, lines 3-4. The attention of the Examiner is further directed to the specification, page 56, lines 17-19, which states: "[t]he present invention is further illustrated by the following specific examples, which should not be construed as limiting the scope or content of the invention in any way." The Examiner alleges that it is improper to "claim specific limitations set forth only in specific examples of the more generic claims of the instant application." Applicants are not aware of such a prohibition, and point to the support for the amendment of Claim 58 found for example at p. 69, lines 3-4.

In view of the foregoing amendments and remarks regarding items A-D of the Office Action, Applicants submit that the new matter rejections do not apply to the claims as presented herein, and respectfully request withdrawal of the rejections.

Rejections Under 35 USC § 102:

Claims 1-13, 15-17 and 53-62 were rejected under 35 USC § 102 (a) or 102(e) as being anticipated by now-abandoned US Patent application publication 2003/0199440 ("'440 publication"), as evidenced by US Patent application publication 2005/0059595 ("'595 publication").

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. MPEP § 2131. Applicants respectfully submit that the '440 publication does not anticipate the invention as claimed because the '440 publication neither teaches nor suggests each and every element of the claimed invention. In fact, the '440 reference teaches away from the claimed invention. Furthermore, even if the '440 publication taught or suggested each and every element of the claimed invention, the '440 publication is not an enabling reference, as discussed below.

The Invention as Claimed:

As stated in the specification, e.g., at page 6, first paragraph:

> The invention provides novel methods and compositions for screening and treating retinal degenerative conditions, including age-related macular degeneration (AMD), as well as animal models useful for testing therapeutic compounds and methods. The invention is the product of a gene discovery strategy resulting in isolation of genes showing differential expression 1) in AMD-affected vs. normal eye tissues and 2) during the process of phagocytosis of outer segments (OS) by RPE cells.

As described throughout the specification and in Examples 1-4, Applicants developed and used a novel macroarray technique (termed "CHANGE") based on an array of 10,000 genes expressed in the RPE/choroid of the eye to discover and isolate genes associated with AMD and/or RPE phagocytosis. Utilizing probes made from isolated RNA from tissues of normal and AMD-affected human eyes to screen the macroarray, Applicants identified at least 200 "genes related to AMD," i.e., "genes

playing a role in the pathogenesis of AMD [that] show changes in expression during the course of the disease." (See, for example, specification at page 60, lines 1-4, and lines 9-25, and page 6, lines 10-12.)

Using probes made from isolated RNA extracted from cultured RPE cells at various stages in the process of phagocytosis of OS *in vitro*, Applicants also screened the CHANGE macroarray system to identify approximately 60 "phagocytosis-related genes," ("genes showing differential expression during the process of phagocytosis of outer segments (OS) by RPE cells"). Genes isolated by this strategy included completely unknown genes and genes previously unknown to be functionally related to the process of OS phagocytosis by RPE cells. See, for example, specification at page 6, lines 1-29. Applicants further showed that in an animal model of retinal degeneration exhibiting overexpression of an AMD/phagocytosis-related gene, i.e., membrane type matrix metalloproteinase (MMP)-1 (MT1-MMP; also known as MMP14), the rate of the retinal degeneration can be delayed by administering an agent that decreases the expression or activity of MT1-MMP (see, e.g., Example 6, page 68).

Accordingly, Claim 1 as originally filed and presented herein recites a method for delaying or reversing a retinal or choroidal degenerative disease or condition in a subject comprising use of "an agent that decreases the expression or activity of an "AMD-related or phagocytosis-related gene." Accordingly, a required element set forth in the treatment method of the instant Claim 1, and claims dependent thereon, is an agent that decreases the expression or activity of an AMD-related or phagocytosis-related gene. One preferred target of the agent, which Applicants have discovered to be upregulated in AMD, is MT1-MMP.

The '440 Publication Does Not Teach or Suggest Decreasing Expression of an AMD-related or Phagocytosis-Related Gene, Does Not Teach or Suggest that MT1-MMP or Any Other MMP is Upregulated in AMD or Any Other Disease of the Eye, and is not an Enabling Reference for Applicants' Claimed Invention.

According to the Office Action (p. 6), the '440 publication anticipates the claimed invention by teaching a method for treatment of damaged tissues associated with age-related macular degeneration (AMD). Applicants respectfully disagree.

Claim 11 of the '440 publication recites a method of therapy comprising administering to a subject a composition as defined in any of claims 1-7 to treat damaged tissue, such as a wound. The composition recited in Claim 1 of the '440 publication comprises a growth factor and an inhibitor agent that can inhibit the action of at least one specific adverse protein (e.g., a specific protease) that is upregulated in a damaged tissue such as a wound environment. Claim 5 of the '440 publication recites an inhibitor agent that is an inhibitor of urokinase-type plasminogen activator (uPA) and/or an inhibitor of a matrix metalloproteinase (MMP).

Paragraphs [0306-308] of the '440 publication state as follows:

> [0306] An essential component of the composition of the present invention is an inhibitor agent. The inhibitor agent may be any suitable agent that can act as an inhibitor of a respective protein (e.g. protease) that is upregulated in a damaged tissue, such as a wound, environment--wherein the protein (protease) has an adverse (deleterious) effect on the healing of damaged tissue.
>
> [0307] The term "inhibitor" means an agent that can reduce and/or eliminate and/or mask and/or prevent the action of a respective protein (e.g. protease) that is upregulated in a damaged tissue, such as a wound, environment--wherein the protein (proteases) has an adverse (deleterious) effect on the healing of damaged tissue.
>
> [0308] Particular inhibitor agents include one or more suitable members of: an inhibitor of uPA (I:uPA), an inhibitor of MMP1 (I:MMP1), an inhibitor of MMP2 (I:MMP2), an inhibitor of MMP3 (I:MMP3), an inhibitor of MMP7 (I:MMP7), an inhibitor of MMP8 (I:MMP8), an inhibitor of MMP9 (I:MMP9),

an inhibitor of MMP10 (I:MMP10), an inhibitor of MMP11 (I:MMP11), an inhibitor of MMP12 (I.MMP12), an inhibitor of MMP13 (I:MMP13), an inhibitor of MMP14 (I:MMP14), an inhibitor of MMP9 (I:MMP15), an inhibitor of MMP16 (I:MMP16), an inhibitor of MMP17 (I:MMP17), an inhibitor of MMP19 (I:MMP19) an inhibitor of MMP20 (I:MMP20), an inhibitor of MMP21 (I:MMP21), an inhibitor of MMP24 (I:MMP24), an inhibitor of MMPFMF(I:MMPFMF).

Thus , the '440 publication describes a vast number of envisioned compositions, each comprising one or more of legion growth factors (see '440 Claims 2-4) in combination with one or more of legion inhibitory agents, including agents with inhibitory activity against gene products of 19 different MMP genes (listed in reproduced paragraph [308] of this publication). Detailed description of specific examples of the hundreds of inhibitory small molecule compounds is provided in over 2500 paragraphs of text of the '440 publication (e.g., see paragraphs [0669] to [3201]).

With regard to a method of therapy using the described compositions to treat damaged tissue ('440 claim 11), the '440 publication (paragraphs [216, 217]) states that use is made of selective inhibitors of adverse proteins (in particular adverse proteases that have a deleterious effect on wound healing) that are upregulated in a damaged tissue, such as a wound, environment, e.g., a chronic wound such as a dermal ulcer.

Remarkably, however, the publication provides (at paragraphs [0641]-[0665]) only one example of a skin wound healing assay in pigs, and this sole *in vivo* example provides no evidence of upregulation of any "adverse protein or protease" in a wound environment and in fact demonstrates that administration of selective inhibitors of the hypothesized upregulated proteases had the opposite to expected effect. The Example concludes (at paragraph [0665]) that "a non-selective MMP inhibitor perturbs wound healing" and that "studies using selective MMP inhibitors (in particular MMP-3 inhibitors) showed no effect on normal wound healing." Thus, the only example relating to a method of treament for wound healing provides no evidence of any involvement of any MMP in wound healing, and no evidence of upregulation of any "adverse protease" in

any damaged tissue, as recited in '440 Claim 1. Furthermore, the publication does not provide any demonstration of a therapeutic benefit of administering a composition comprising an MMP inhibitor to a healing skin wound, which was the only medical condition tested. In fact, the scant *in vivo* data in the '440 publication demonstrate that the only non-selective MMP inhibitor to be tested was deleterious to skin wound healing, and that selective MMP inhibitors had no effect in this model based on skin wounding. For reasons cited above, this publication is clearly not an enabling reference for an effective method of treatment using an agent that inhibits a protease, and in fact would discourage one skilled in the art to try to develop such a therapy.

Despite the negative results described in Example 2, the '440 publication (at paragraph [218]) states as follows:

> [0218] In addition, or in the alternative, the damaged tissue environment for treatment may be one or more those associated with age-related macular degeneration, corneal ulceration, corneal melting, irritable bowel syndrome/disorder/disease, gastric ulceration, renal failure, peripheral neuropathies (e.g. diabetic retinopathy), neurodegenerative diseases, bone diseases or injury, cartilage diseases or injury, muscle diseases or injury, tendon diseases or injury, ischaemic damage, peridontal disease, psoriasis, bullous pemphigoid, epidermolysis bullosa, spinal cord disease or injury.

Thus, without providing any supportive evidence therefor, the '440 publication states that the myriad compositions described in the publication can be used for treatment of a large number of categories of diseases affecting nearly every major system of the body, including the nervous (including visual), musculoskeletal and dental, gastrointestinal, renal, cardiac, and integumentary systems.

More particularly, with regard to disorders involving retinal degenerations, the '440 publication is completely silent as pertaining to Applicants' claimed method for delaying or reversing a retinal or choroidal degenerative disease or condition such as AMD using an inhibitor of a specific MMP, for example using an agent that

downregulates the expression or activity of MTI-MMP/MMP14, as claimed in the instant invention. The one and only reference to AMD to be found in the '440 publication is among the long list of diseases and disorders provided in paragraph [218], reproduced *supra.*

Furthermore, the '440 publication provides no teaching from the prior art that would motivate one of skill in the art to predict that an inhibitor of an MMP would be useful for therapy of any eye disease. In fact, eye diseases are completely absent from the list of conditions in which MMPs are said to be important, as provided in paragraph [0235] of the '440 publication, which states in pertinent part:

> [0235] ... Examples of conditions where MMPs are thought to be important are those involving bone restructuring, embryo implantation in the uterus, infiltration of immune cells into inflammatory sites, ovulation, spermatogenesis, tissue remodelling during wound repair and organ differentiation such as such as in venous and diabetic ulcers, pressure sores, colon ulcers for example ulcerative colitis and Crohn's disease, duodenal ulcers, fibrosis, local invasion of tumours into adjacent areas, metastatic spread of tumour cells from primary to secondary sites, and tissue destruction in arthritis, skin disorders such as dystrophic epidermolysis bulosa, dermatitis herpetiformis, or conditions caused by or complicated by embolic phenomena, such as chronic or acute cardiac or cerebral infarctions

Thus the '440 publication is also not enabled for a method of delaying or reversing a retinal or choroidal degeneration as recited in Applicants' Claim 1 and claims dependent thereon. Rather it is Applicants, through use of their novel gene expression strategy designed to identify genes showing changes in expression in AMD-affected eyes and during phagocytosis by cultured RPE cells who discovered the unexpected and heretofor unknown involvement of MT1-MMP in RPE phagocytosis and in AMD and other retinal degenerations.

For reasons discussed above, whereas the '440 publication discloses an impressive number of inhibitory compounds including many MMP inhibitors, it provides no experimental basis, teaching or motivation, or enablement for use of any MMP inhibitor to treat any medical condition beyond what was generally known in the prior art. More specifically, the reference provides no experimental basis, general teaching or motivation to use an agent that downregulates the expression or activity of the specific MMP gene of the instantly claimed invention, i.e., MT1-MMP (MMP14). Furthermore, the reference clearly does not provide any enablement, or teaching or suggestion (beyond the opportunity for mere keyword matching from among the hundreds or thousands of possible combinations of listed growth factors, inhibitors and diseases, to arrive at the claimed invention) of Applicant's discovery that downregulation of MT1-MMP can be useful in the treatment of a degenerative eye disease such as AMD.

Additionally, the '440 publication does not teach or suggest anything regarding the claimed phagocytosis-related genes, or a relationship of these genes to any disease or condition. Phagocytosis is not even mentioned in the '440 publication.

Accordingly, Applicants respectfully submit that at the least the '440 publication does not anticipate or render obvious the Claim 1 elements of downregulating expression of MT1-MMP for a therapeutic purpose (delaying or reversing a retinal degeneration); or downregulating expression of a phagocytosis-related or AMD-related gene, as disclosed and instantly claimed.

Furthermore, the '440 publication does not provide any teaching or motivation to contact the claimed cell types of the eye (retinal, choroidal cells) with an agent that downregulates expression or activity of an AMD-related or phagocytosis-related gene. Therefore, the '440 publication clearly does not anticipate each and every element of the claimed invention.

The deficiencies of the '440 publication with respect to § 102 rejections of Claims 9, 12, and 54-62 are not remedied by the '595 publication, a post-filing (2005) reference used by the Examiner to support an argument that intraocular injection can inherently

allow diffusion throughout the vitreous, retina, and choroid. Any consideration of that question is moot, however, because the '595 publication does not supply any of the necessary claim elements missing from the '440 publication (such as phagocytosis-related genes, or downregulation of MT1-MMP). These missing elements are not even mentioned in the '595 publication, which relates to compositions comprising proteins irrelevant to the instant applications, i.e., ADP-ribosyl transferase fusion proteins (Abstract, '595 publication).

Therefore, the '595 publication does not bolster a 35 USC §102 (or § 103) rejection of the claimed invention based on the '440 publication, which as discussed cannot stand alone. Further, even if it disclosed one or more of the missing elements, the '595 publication would be an improper reference under either §§ 102 or 103 because it is not a proper prior art reference, given its publication date of March 17, 2005.

For all of the reasons presented, Applicants submit that the invention as claimed is not anticipated by the cited references and respectfully request withdrawal of the rejections of Claim 1, and claims dependent thereon, under 35 USC § 102.

CONCLUSION:

In view of the amendments and arguments presented herein, Applicants believe the pending application is in condition for allowance. Early and favorable action on the application is respectfully requested. If the Examiner believes an interview would expedite prosecution to allowance, the Examiner is cordially invited to call the undersigned at the number indicated.

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Respectfully submitted,

By _____

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